Imaging Biomarkers in Radiation Oncology and Beyond: Development, Evaluation and Clinical Translation

Imaging Biomarker Roadmap for Cancer

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DISCLOSURES & CONFLICT OF INTEREST. John Waterton holds stock in Quantitative Imaging Ltd and receives compensation from Bioxydyn Ltd, a for-profit company engaged in the discovery, development, provision and marketing of imaging biomarkers.
Biomarker:
A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.

Categories of biomarkers include:
• susceptibility/risk biomarker
• diagnostic biomarker
• monitoring biomarker
• prognostic biomarker
• predictive biomarker
• pharmacodynamic/response biomarker
• safety biomarker
Six key cancer imaging modalities

- PET
- SPECT
- Xray, DEXA, CT
- Optical, NIR
- MRI/S
- ELECTROMAGNETIC WAVES, PHOTONS
  - pm
  - nm
  - µm
  - mm
  - m
  - MeV
  - keV
  - eV
- ELECTRIC, MAGNETIC FIELDS
  - GHz
  - MHz
- PRESSURE WAVES (SOUND)
  - GHz
  - MHz
  - ultrasound
<table>
<thead>
<tr>
<th>Metrology definition</th>
<th>Colloquial definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordered categorical (incl. binary)</td>
<td>How ugly?</td>
<td></td>
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<tr>
<td>Extensive</td>
<td>How big?</td>
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<tr>
<td>Ordered categorical (incl. binary)</td>
<td>How ugly?</td>
<td>• TNM stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ACR BIRADS breast morphology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ⁹⁹mTc-etarfolatide FR+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiomic signature of heterogeneity</td>
</tr>
<tr>
<td>Extensive</td>
<td>How big?</td>
<td>• LVEF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spleen volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• circumferential resection margin in rectal cancer</td>
</tr>
<tr>
<td>Intensive</td>
<td>How hot?</td>
<td>• SUV&lt;sub&gt;max&lt;/sub&gt;⁵¹¹In-pentetrotide</td>
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<td>• SUV&lt;sub&gt;max&lt;/sub&gt;¹⁸F-fludeoxyglucose</td>
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<tr>
<td></td>
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<td>• Aprepitant receptor occupancy %</td>
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<td></td>
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<td>• $\Delta K^{\text{trans}}$ gadoterate</td>
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<tr>
<td></td>
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<td>• DCE-US AUC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MRI ADC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• $^{13}$C-pyruvate $k_p$</td>
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</tbody>
</table>
Problem statement: imaging biomarkers in cancer

- Not a new idea – predates molecular biology!
  - Tumour size: 1940s/50s
  - Tumor $T_1$ (1971) led to invention of MRI
  - Exemplified in FDA/NIH biomarker workshop (1999)

- Today used routinely – all BEST categories
  - Cancer drug development
  - Regulatory approval
  - Routine oncologic practice

- Many investigational imaging biomarkers in cancer
  - Disappointing rate of translation – why?
Biospecimen removed from patient
molecule or cell analyte detected with *in vitro* Diagnostic Device

**biofluids**
- urine
- blood
- exhalate
- sputum
- saliva
- semen
- faeces
- synovial fluid
- CSF
- etc

**solid tissues**
- cervical smear
- skin biopsy
- hair follicle
- buccal biopsy
- liver biopsy
- bone biopsy
- synovial biopsy
- tumour biopsy
- excised tumour
- etc

Biosignal measured in vivo
signals detected by *in vivo* Diagnostic Device

**electromagnetic fields & photons**
- PET
- SPECT
- CT, XR
- endoscopy
- fluorescence
- MRI/S
- ECG
- EEG
- MEG
- etc

**sound & pressure**
- ultrasound
- infrasound
- palpation
- auscultation
- plethysmography
- spirometry
- etc

 imaging
- electrophysiology
- physiologic measurement
- wearables/smartphones
- etc

...molecular, histologic, radiographic, or physiologic characteristics...
<table>
<thead>
<tr>
<th>Imaging biomarker:</th>
<th>Biospecimen biomarker:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner in hospital Radiology Dept</td>
<td>In vitro diagnostic device</td>
</tr>
<tr>
<td>Different scanners from different</td>
<td>Identical IVDDs</td>
</tr>
<tr>
<td>vendors installed in different</td>
<td></td>
</tr>
<tr>
<td>hospitals</td>
<td></td>
</tr>
<tr>
<td>Scanners not designed, maintained or</td>
<td>IVDDs designed, maintained and</td>
</tr>
<tr>
<td>approved for measuring biomarkers</td>
<td>approved for specific measurement</td>
</tr>
<tr>
<td>Main job role not quantitation</td>
<td>Trained, dedicated staff</td>
</tr>
<tr>
<td>Quality depends mainly on events at</td>
<td>Quality depends mainly on the</td>
</tr>
<tr>
<td>the moment of scanning</td>
<td>central lab</td>
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<tr>
<td>Picture quality drives innovation:</td>
<td>Stable platform due to regulatory</td>
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<tr>
<td>unpredictable effect on quantitation</td>
<td>approval</td>
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<tr>
<td>Seldom defined analytes</td>
<td>Defined molecular entity via</td>
</tr>
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<td>analytical biochemistry</td>
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Stable platform due to regulatory approval
Typical biospecimen biomarker validation roadmap

- Molecule of biological interest ("analyte")
- Biospecimen

Flowchart:
- Assay development
- Assay validation
- Clinical validation
- Clinical utility
http://dx.doi.org/10.1038/nrclinonc.2016.162

Includes supplementary files

- Problem statement
- Examples – all modalities and contexts of use
- Definitions
- Detailed roadmap
- Recommendations

Imaging biomarker roadmap for cancer studies

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Abstract | Imaging biomarkers (IBs) are integral to the routine management of patients with cancer. IBs used daily in oncology include clinical TNM stage, objective response and left ventricular ejection fraction. Other CT, MRI, PET and ultrasonography biomarkers are used...
Figure 2: The imaging biomarker roadmap

O'Connor, J. P. B. et al. (2016) Imaging biomarker roadmap for cancer studies
Figure 1 Overview of the imaging biomarker roadmap

O'Connor, J. P. B. et al. (2016) Imaging biomarker roadmap for cancer studies
### Key perspectives

<table>
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<tr>
<th>Technical validation, clinical validation, clinical utility</th>
<th>Imaging (biosignal) bm</th>
<th>Typical biospecimen bm</th>
</tr>
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<tbody>
<tr>
<td>Technical validation, clinical validation, clinical utility</td>
<td>Iterative in parallel</td>
<td>Mainly in series</td>
</tr>
<tr>
<td>Biological and clinical validity</td>
<td>Biological validation platform of evidence e.g. Bradford Hill criteria</td>
<td>Definitive clinical outcome studies e.g. Kaplan Meier</td>
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Roadmap recommendations

1. Align grants and publications to roadmap
2. Exhaustively document methodology in publications
3-7. Technical (assay validation)
   - Consensus, accreditation, repeatability, reproducibility, analysis methodology
8-11. Biological and clinical validation
   - Platform of evidence (Bradford Hill criteria)
   - Imaging-pathology correlation (human and animal)
   - Data sharing
   - Publication bias
12. Design of outcome studies
13-14. Cost effectiveness and clinical utility
   - Imaging agents pricing; QALY advantage
The problem of poorly aligned incentives

- Standardisation not considered innovative by funding agencies nor career-enhancing for academics
- Novel biomarker can’t be used without reliable accurate measurement.
- Not a good use of vendors’ resources to provide accurate measurement unless demand from customers (radiologists)
- Can’t acquire evidence base unless scanners routinely generate accurate measurements
- Radiologists won’t demand accurate measurements without evidence from multicentre trials to show impact of measurement on health outcomes.
Incentivisation through public-private partnerships, professional bodies

- Standardising FDG-PET, FLT-PET, MRI-ADC, MRI-$K^{\text{trans}}$, MRI-DIILD etc

Innovative approaches to incentivisation

Academics innovate, businesses standardise